

# Brachytherapy in the treatment of lung cancer – a valuable solution

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## Abstract

The majority of patients with lung cancer are diagnosed with clinically advanced disease. Many of these patients have a short life expectancy and are treated with palliative aim. Because of uncontrolled local or recurrent disease, patients may have significant symptoms such as: cough, dyspnea, hemoptysis, obstructive pneumonia, or atelectasis. Brachytherapy is one of the most efficient methods in overcoming difficulties in breathing that is caused by endobronchial obstruction in palliative treatment of bronchus cancer. Efforts to relieve this obstructive process are worthwhile, because patients may experience improved quality of their life (QoL). Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease as well as in the postoperative treatment of small residual peribronchial disease. Depending on the location of the lesion, in some cases brachytherapy is a treatment of choice. This option is fast, inexpensive, and easy to perform on an outpatient basis.

Clinical indications, different techniques, results, and complications are presented in this work.

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**Key words:** brachytherapy, bronchial cancer, endoluminal, interstitial, lung cancer.

## Purpose

Lung cancer is an ever-increasing health problem, smoking habits being responsible for a major increase in incidence in recent decades, and with five-year survival rates reaching only 10-12% during the last 20 years. The lung cancer failure rate remains unacceptably high, despite major advances over the past 40 years in the field of surgery, radiotherapy, and chemotherapy. In general, upon diagnosis, 25-30% of the non-small cell lung cancer (NSCLC) patients present with tumors confined to the lung (stage I or II), and only 40-50% of them can be targeted for cure; 30% have locally advanced disease (stage III), the remaining 40-45% have distant metastases (stage IV). Local recurrences after external beam radiotherapy (EBRT) occur in 60-70% of patients, and are responsible for 60% of the mortality due to respiratory failure, obstructive pneumonia, and sepsis. One of the most distressing symptoms for lung cancer patients is airway obstruction [1].

Brachytherapy (BT) plays an important role in the palliative treatment of obstructive disease, sometimes in conjunction with endobronchial laser therapy or stent implantation. Removal of endobronchial obstruction leads to quick improvement of clinical status and Quality of Life (QoL) [2-9]. Depending on the location of the lesion, in some cases, brachytherapy is a treatment of choice.

Efforts to relieve this obstructive process are worthwhile, because patients may experience improved QoL in hours or next days after treatment. In most cases, BT has a palliative aim due to advanced clinical stage [10-13]. Lack of clear consensus regarding the value of doses used in BT is the reason why different fraction doses are used in clinical treatment [1]. Due to bad performance status (Zubrod-ECOG-WHO score  $\geq 2$ ), single high doses ranging from 10 Gy to 15 Gy are applied [14,15]. It seems that results in this procedure are similar to whenever doses were given weekly in two or three fractions. A single dose protocol is cost-saving procedure and more comfortable for patients [6]. On the other hand, weekly repeated treatment enable to achieve a better local control visualized with the use of bronchoscopy. Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease, in selected advanced inoperable tumors combined with EBRT or in the postoperative treatment of small residual peribronchial disease [16]. A relatively rare indication is interstitial BT of peripheral tumors using permanent implants.

## General rules

High-dose-rate brachytherapy (HDR-BT) of lung cancer is a well-established method for the local treatment of patients with inoperable tumors of the tracheobronchial

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system. In order to palliate symptoms and improve the quality of the remaining life for these patients, it is preferable to use a method that is relatively easy to perform and has minimal complications. Removal of the tumor mass by endoscopic biopsy forceps combined with cryosurgery, electrocautery, or laser ablation can achieve only limited clearance and short-term palliation, because the tumor kinetic is not altered [1]. Therefore, HDR-BT is the option of treatment endobronchial tumors, which can increase the efficiency of the control of malignant airway obstruction and the duration of palliation [17]. By placing a radioactive source near or in the tumor, a high dose of radiation is given to the tumor with the dose fall off in accordance of the inverse square law (Figure 1) [18]. The chance of damaging healthy tissues is reduced, since only a small amount of tissue receives therapeutic dose of radiation. The advantages of this technique over EBRT are: 1) it can be performed on an out-patient basis, 2) it decreases radiation exposure of the staff, 3) it permits optimization of dose distribution, 4) the treatment time is short, measured in minutes, 5) it reduces healthy tissue damages, caused by rapid dose fall off, which is particularly important for previously irradiated area.

As mentioned before, the leading clinical symptoms are dyspnoea, cough, haemoptysis, and pain. Some of patients show more than one symptom at diagnosis. The symptoms are qualified according to Speiser and Spratling scale for assessing palliative response in endobronchial brachytherapy [13]. An airway obstruction that is secondary to extensive primary or recurrent intrathoracic cancer, occurs frequently and creates devastating effects for many patients.

The definitive decision for brachytherapy is based on clinical examination, flexible bronchoscopy with precise documentation of the location and the amount of obstruction, and X-ray of the chest, which in some cases is supplemented by computed tomography or endobronchial echography. It is important to determine tumor extent as clearly as possible. For curative treatments, a comprehensive work up, as it is typical for lung cancer, should

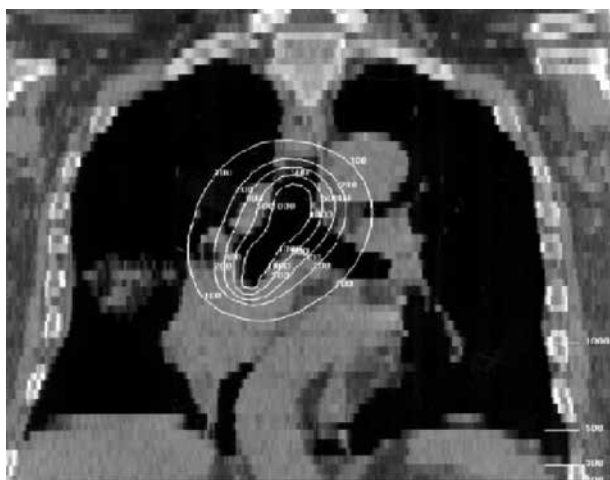


Fig. 1. Coronal reconstruction plane with superimposed dose distribution achieved with dose prescription relative to the mucosa. Rapid dose-fall visible [18]

be performed, including in each case computed tomography (CT) and/or magnetic resonance imaging (MRI) of the chest and appropriate investigations such as positron emission tomography-computed tomography (PET-CT) to exclude distant and lymph node metastases.

## Clinical indications

### Radical treatment

Indications include:

1. Postoperative external radiotherapy and/or intraluminal brachytherapy of the bronchial stump after resection with positive resection margins [16].
2. Endobronchial brachytherapy with curative intent is considered as a boost for minor residual disease within a combined non-surgical radical approach. This may apply to small cell lung cancer after remission induction by chemotherapy and external radiotherapy or for non-small cell lung cancer as a boost after remission induction by external beam radiotherapy (with or without chemotherapy) [19,20].
3. Definitive radiotherapy and brachytherapy [21,22] or brachytherapy alone for small tumours (T1-T2) [3,4,23-27].

Commonly used treatment schemas are listed in Table 1.

### Palliative treatment

Indications include:

1. Irradiation of tumors causing significant complaints, mainly dyspnoea caused by endobronchial obstruction, cough, haemoptysis, bronchopneumonia, and atelectasis [1,6,7,10,30-33].
2. Brachytherapy in recurrences after surgery and/or EBRT [1,6,7,30-33].
3. Irradiation of metastasis obturating bronchi. Brachytherapy can be performed as sole treatment or can be combined with EBRT (massive lymph node involvement), laser resection, implantation of prosthesis, and cryotherapy.

Doses used in palliative HDR-BT are also listed in Table 1.

## Contraindications

General remark – decision must be taken individually. Most commonly cited contraindications for brachytherapy include peripheral tumor location, Pancoast tumor (in some cases interstitial brachytherapy can be used), external pressure (e.g. lymph node compression), contraindications for bronchoscopy (rare). General criteria include: WHO  $\geq 2$ , lack of histopathological diagnosis (despite of poor general condition and intensive dyspnoea), tumor location not achieved during bronchoscopy [6,7,17,34]. In many cases brachytherapy is a saving-life procedure.

## Brachytherapy techniques [1]

### Endobronchial brachytherapy

In order to evaluate the airway, locate the tumor size, and define the site of obstruction, an initial bron-

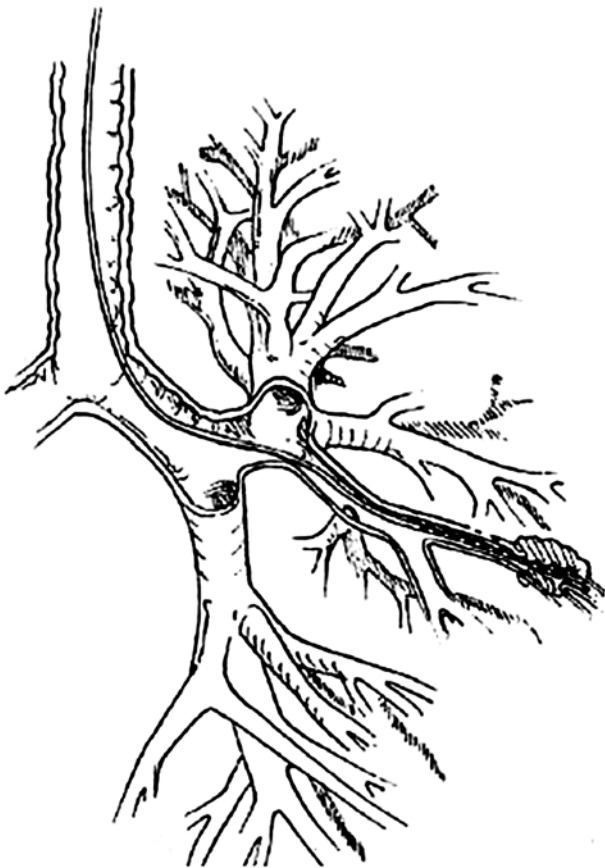
**Table 1.** Brachytherapy treatment schemas – indications, doses [1,28,29]

Indications for brachytherapy	I clinical phase	II clinical phase	III clinical phase	IV clinical phase
Radical combined treatment: schema I; Clinical stage T1-3 N1-3 M0	EBRT: total dose 44 Gy in 22 fr. aa 2 Gy (2 a-p fields)	1 fr. × 6 Gy	EBRT 16 Gy in 8 fr. (changed fields)	1 fr. × 6 Gy
Radical combined treatment: schema II; Clinical stage T1-3 N1-3 M0	EBRT: total dose 44 Gy in 22 fr. aa 2 Gy (2 a-p fields)	EBRT 16 Gy in 8 fr. (changed fields)	HDR-BT - in 1, 3 and 5 week of EBRT – 3 fr. × 10 Gy	
Radical sole treatment, radio- logically occult cancer T1-2N0	Total dose 36-42 Gy in 6-7 fr. with interval of 4-7 days between fractions			
Radical treatment after surgery – R2	After EBRT with total dose of 50-60 Gy	To consider increas- ing the total use using HDR-BT HDR. Fr. dose from 1 × 6 Gy till 3 fr. × 6 Gy (18 Gy), depending on EBRT dose		
Radical treatment: stump infiltration	Sole brachytherapy: 4 fr. of 7.5-10 Gy with interval of 4-7 days between fractions			
Palliative treatment	Total dose 18 Gy in 3 fr. of 6 Gy with interval of 4-7 days – in patients treated earlier with EBRT – dose > 50 Gy			
	Total dose 22.5 Gy in 3 fr. of 7.5 Gy with interval of 4-7 days – in patients not irradiated or treated earlier with EBRT – dose < 50 Gy			
	1 × 10 Gy in case of WHO scale > 2 Sometimes dose can be repeated after few weeks, in cases with clinical remission or visible during bronchoscopy			

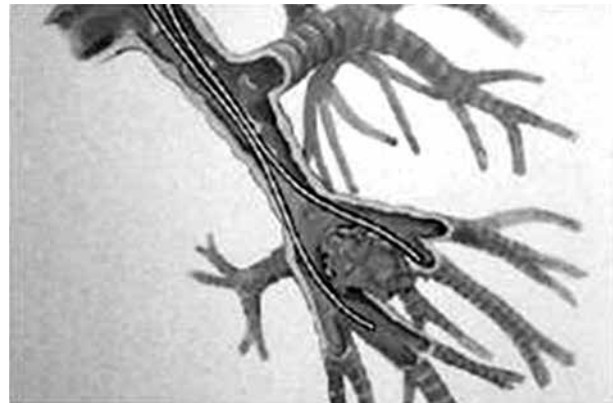
EBRT – external beam radiotherapy, HDR-BT – high-dose-rate brachytherapy, fr. – fraction, a-p – anterior-posterior fields

choscopy in local anesthesia is performed. Premedication is to provide anxiolytic drugs (e.g. midazolam 2.5 mg subcutaneous), parasympatric blocking agent (often atropine 1 mg), and antitussive drug (often codeine). The catheters (one or two, either a 5- or 6-French) used to deliver the brachytherapy should be inserted through the brush channel of the bronchoscope (Figure 2 and 3). If a 6-French catheter is used, a large bronchoscope with brush channel diameter of at least 2.2 mm is required. If the HDR source has to pass tight curves, it is not possible with the 5-French catheter and the use of a 6-French catheter is necessary. If the bronchoscope is connected to a teaching head or a video monitor, the physician performing the application can visualize the lesion and the catheter. For the patient's comfort and to secure the catheter, the bronchoscope should be inserted through the nose. Then the afterloading catheter is inserted through the brush channel of the bronchoscope, passes through the tumor, and is lodged in one of the smaller bronchi. It is recommended to perform a fluoroscopic confirmation of the catheter's position. Then the distance between the proximal extent of the tumor and fixed structures such as the carina is measured. While the radiation oncologist pushes the catheter in, the assisting physicist or nurse (depending of local organization) carefully withdraws the bronchoscope. The use of fluoroscopy helps to keep the catheter in place during this push-pull technique of bronchoscope removal. The catheter should be secured

with tape at the nose, and its position is marked in ink to alert the medical staff in case of displacement. In some situations (tumor localized in the carina of the main bronchi or smaller bronchi), multiple catheters (mostly two) are to be used. In such case, the procedure is repeated, making sure to clearly mark and describe each catheter. Localization X-rays with radio-opaque dummy wires in the catheter are then obtained Figures 4 and 5. To determine the length to be irradiated and the initial dwell position, the location of the obstruction and the target length are marked on the X-rays (in palliative treatment planning). The length to be irradiated usually covers the endobronchial tumor and ± 2.0 cm proximal and distal margins. The dose has been commonly prescribed at 1 cm from the source, although various points from 0.5 to 2 cm are used. If standard lengths and doses are used, the whole time of brachytherapy procedure can be shortened by starting treatment without any delay. When a single catheter is used and if there is minimal curvature in the area to be irradiated, it is possible to minimize the treatment planning time by using pre-calculated standard treatment plans for 3-10 cm lengths to be irradiated from 5 to 10 Gy at 1 cm from the source using equal dwell times. However, individualized image-based treatment planning must be performed if multiple catheters are used [35,36]. Examples of implanted catheters in bronchi are presented in Figures 6 and 7.



**Fig. 2.** Endobronchial brachytherapy with a small (< 2 mm, 5- to 6-French) endobronchial applicator, entered in a tertiary bronchus for treatment [17]



**Fig. 3.** Intraluminal technique with two tubes in bronchus brachytherapy: schematic anatomical diagram showing the ideal situation with two tubes encompassing a small tumor located in the carina of two tertiary bronchi in the left lower lobe [17]

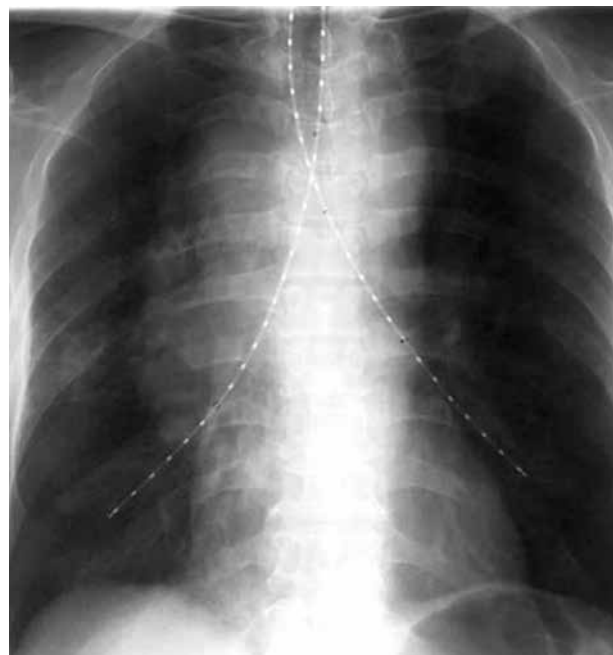
### *Interstitial brachytherapy [1]*

#### *Permanent implants brachytherapy*

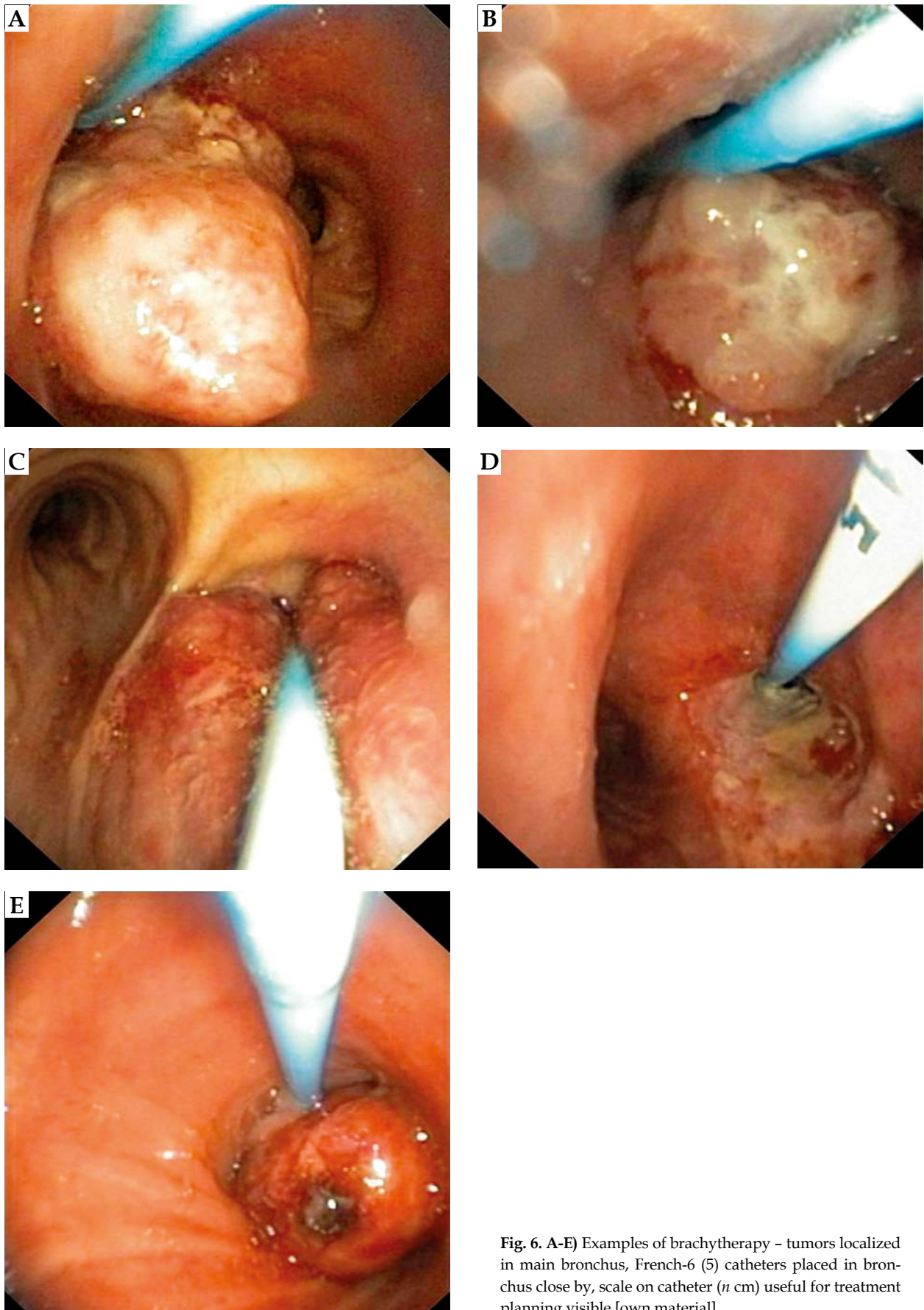
In peripheral tumors, inoperable for different reasons and inaccessible in bronchofiberscopy, some percutaneous techniques may be applied [37-44]. This techniques are used occasionally, mainly in some academic centers in US and Japan. Patients affected by carcinoma of the lung many times have limited pulmonary capacities, either from long-term damage due to a significant past history of smoking or any one of a number of physiologic reasons. These patients may not tolerate traditional thoracotomy and lobectomy. Potential treatment options for



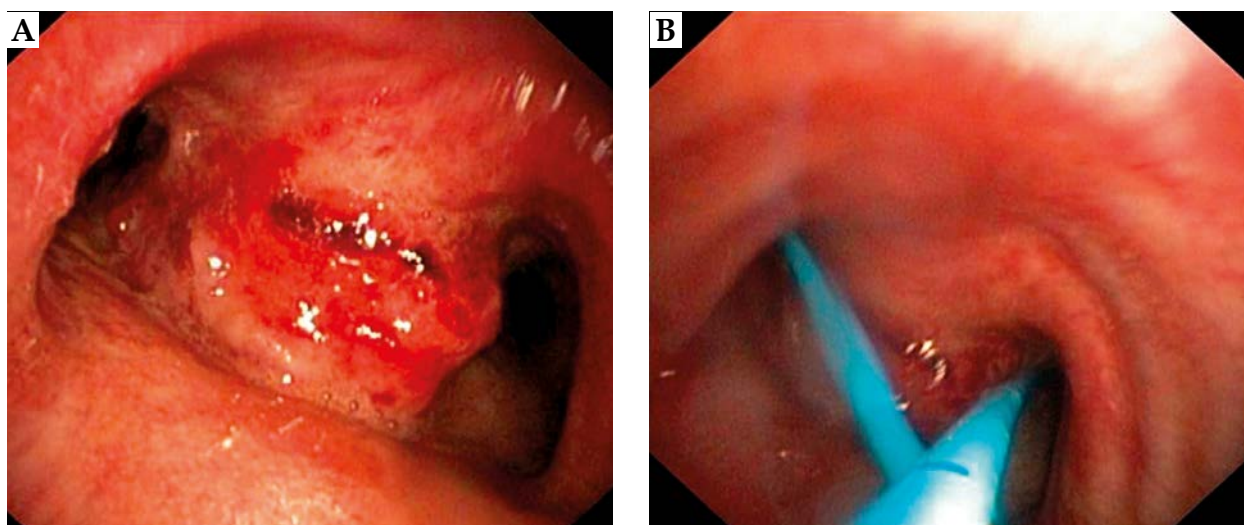
**Fig. 4.** Endobronchial applicator with metal marker inside used for treatment planning, tumor localized in left upper lobe bronchus, X-ray picture [own material]



**Fig. 5.** Bilateral lung cancer - endobronchial applicators with metal markers inside used for treatment planning, tumor localized infiltrating carina and both main bronchus, X-ray picture [own material]



**Fig. 6. A-E** Examples of brachytherapy – tumors localized in main bronchus, French-6 (5) catheters placed in bronchus close by, scale on catheter (*n* cm) useful for treatment planning visible [own material]



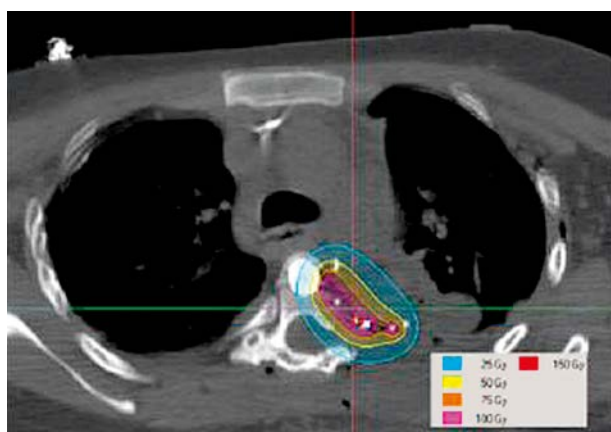
**Fig. 7. A, B)** Tumor infiltrating carina and both main bronchi before application and after application of two brachytherapy catheters. In this cases, irradiated area includes carina and both main bronchi [own material]

these high-risk or medically inoperable patients include sublobar resection with or without  $^{125}\text{I}$  lung brachytherapy [44]. Permanent implantation of  $^{125}\text{I}$  seeds can be safely used in areas where the total dose of radiation received is usually limited by significant late toxicity, such as directly on pulmonary tissue or in close proximity to the spinal cord. Published studies describe the use of intraoperative, permanent implantation of  $^{125}\text{I}$  seeds for the treatment of thoracic malignancies. In early-stage of NSCLC, the addition of intraoperative brachytherapy to sublobar resection improved predicted rates of local control, and overall survival compared to sublobar resection alone. In more advanced disease with residual tumor or positive lymph nodes at surgery, the addition of thoracic brachytherapy resulted in favorable rates of local control and survival. When planar  $^{125}\text{I}$  implants were placed following resec-

tion of metastatic and locally invasive paraspinal tumors, excellent local control rates with minimal toxicity were seen, despite high localized doses to the spinal cord [37]. Most frequently isotopes  $^{125}\text{I}$ ,  $^{103}\text{Pd}$ , and  $^{131}\text{Cs}$  (dose rate 0.01 to 0.3 Gy/h) are used (Figure 8 and 9). Physical characteristics of them shows low-energy, small size, and short half-life decay time. Treatment time doesn't exceed 30-45 minutes, isotopes are implanted into tumor in total analgesia. Special elastic applicators are used for implantation. Nominal total activity is 0.5-1 Gy/h, total summarized dose is 100-160 Gy in CTV (clinical target volume). Recommended diameter of the tumor should not exceed 5-6 cm. This technique is used in subpleural, peripheral tumors or Pancoast tumor [1].

#### *Temporary high-dose-rate brachytherapy*

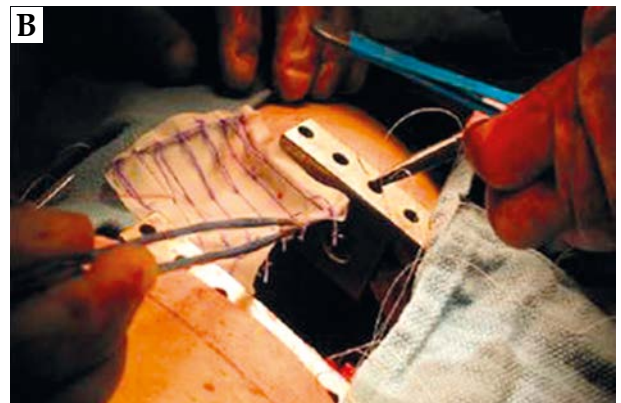
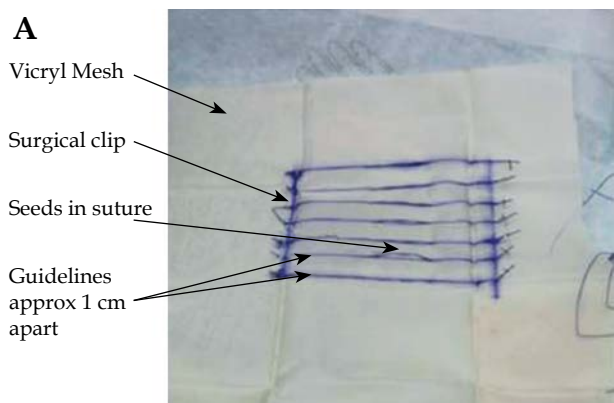
An alternative for permanent brachytherapy could be interstitial brachytherapy with the use of HDR sources. Sometimes the costs are the most important reason for choosing this technique. If permanent implants are not available, in one procedure elastic applicators (using steel needles first) are inserted into tumor tissue. After preparing a treatment plan, a patient is connected to the HDR unit and irradiated. High-dose-rate brachytherapy is used in tumors smaller than 2 cm in diameter. One fraction of 10-20 Gy was used so far (Figure 10). After not complete tumor excision, elastic applicators can be fixed in tumor bed. Three to seven days after surgery HDR-BT is performed, 3-4 fractions of 4-5 Gy are used (one fraction daily) [40,41,45,46].



**Fig. 8.** Axial isodose distributions for a planar permanent  $^{125}\text{I}$  paraspinal implant. Intraoperative  $^{125}\text{I}$  seed placement has been used in conjunction with sublobar resection in patients with lung cancer who are medically unfit for lobar resection. This technique is currently being evaluated in the USA in a multi-institution randomized prospective trial by the American College of Surgeons Oncology Group (ACOSOG) Z4032 [41]

#### **Target volume and planning**

The intraluminal target volume is usually determined by bronchoscopy findings. Proximal and distal margins of the intraluminal gross tumor volume must be carefully assessed and the distance from both margins to the tracheal carina measured. In completely obstructing lesions, assessment of the distal margin may not be possible by endosco-



**Fig. 9.** **A)** Planar implant made using  $^{125}\text{I}$  seeds in suture within a Vicryl mesh. **B)** Completed implant being placed into mediastinum using long-handled tools. The seeds will be straightened to give optimal dosimetry before lung reinflation [41]

py. Additional information from chest X-ray or CT imaging may be helpful to estimate the length of the obstruction.

Since in palliative brachytherapy the extraluminal part of the tumor is usually rather large, and therefore not treatable by brachytherapy, there is only limited need for a precise assessment of the extraluminal tumor dimensions for target definition. In the longitudinal direction, a safety margin of 2 cm is usually added to both sides of the macroscopic tumor to define the target volume. If there is a doubt regarding the distal margins, an extra 2 to 3 cm should be added to insure covering the whole endobronchial tumor extension.

In contrast, in curative brachytherapy, the whole area at risk must be included. This is the wall in superficial spreading tumors, and tumor depths of a few mm in limited T1-tumours. Autofluorescent bronchoscopy is very helpful in this case, determining exactly the margins of the infiltrating tumor. The same applies for adjuvant treatment after radical resection with positive margins, and for minimal residual disease after chemotherapy and/or external beam therapy.

Computed tomography scans with the applicator in place allow a better estimate of the tumor topography in relation to the applicator. CT-based planning enabling more precise target volume definition and volumetric dose information can improve the therapeutic ratio of brachytherapy (Figures 11). Potential benefits and limitations of using CT-assisted brachytherapy can be characterized by the following:

1. Use of CT imaging to supplement the findings of bronchoscopy, particularly in determining the distal extent of the target volume.
2. Visualization of the position of the applicator in relation to the target volume.
3. Facilitation of dose prescription to the bronchial mucosa by identifying the position of branching of the different sub-segments of the bronchial tree, and allowing the use of actual measurements of the diameter of each segment.
4. Visualization and delineation of the esophagus, particularly in tumors of the trachea and the left primary bronchus.
5. Generation of a 3D dosimetric database for correlation with toxicity [18,25,35,36,47-49].



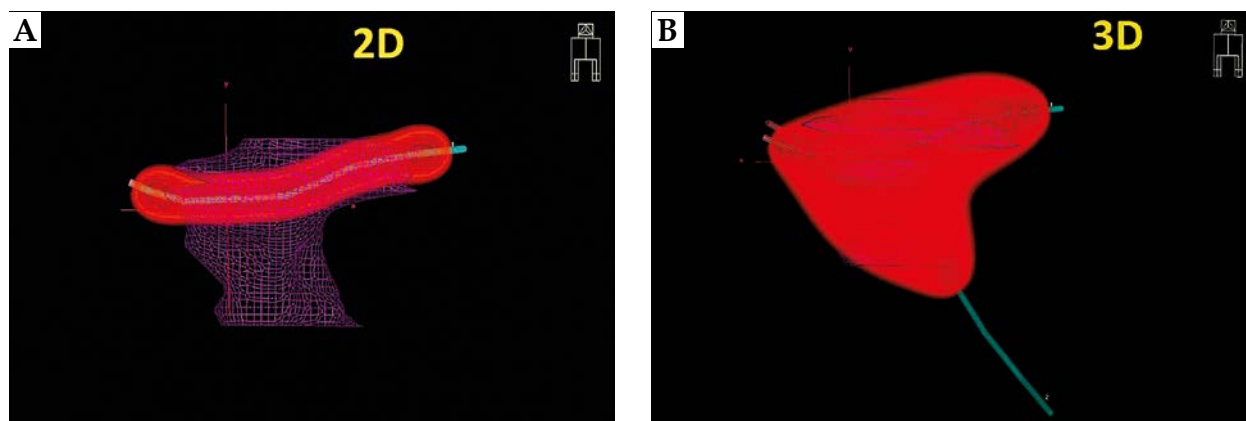
**Fig. 10.** Lung metastasis of colorectal carcinoma treated with a single brachytherapy catheter. The inner isodose represents 20 Gy. Note the steep gradient with the outer isodose, illustrating a dose of 3 Gy [46]

## Results

### *Monotherapy - radical treatment*

Survival after treatment in M0 patients seems to be dependent on the degree of remission achieved. Macha *et al.* [50] reported a mean survival of 7.5 months in M0 patients ranging from 8.5 months in PR to only 2.5 months (NC + PD). However, the impact of endobronchial BT on survival is still debatable. Speiser and Spratling [13] reported that patients treated with curative intent with EBRT and a BT boost did not have a significantly longer survival than patients treated with EBRT alone.

The Munich group [20] conducted a prospective randomized trial on central lung tumors. Patients received 60 Gy with EBRT and received either no further treatment or a boost of two 4.8 Gy endobronchial HDR fractions at 10 mm from the source axis. The median local control in these advanced cases was increased with the boost from 12 weeks to 21 weeks ( $p = 0.052$ ). In the 68 patients with squamous cell carcinoma, the impact of the boost was more important with a significant increase in local control ( $p = 0.007$ ). Survival time seemed to be lon-



**Fig. 11. A)** Patient with two catheters inserted during regular 3D planning. For the 2D planning only one of them would be used (the one inserted into the bronchus with visible obturation). Comparison of GTV coverage by the 90% isodose achieved in 2D planning system. Legend: purple triangles – GTV volume, orange cylinder – 2D 90% isodose, blue – catheter. **B)** Patient with two catheters inserted. Comparison of GTV coverage by the 90% isodose achieved in 3D planning system. Legend: purple triangles – GTV volume, orange volume – 3D 90% isodose, blue – catheters [36]

ger (40 vs. 33 weeks) but did not reach statistical significance ( $p = 0.09$ ).

A specific subgroup to be considered is radiographically occult endobronchial tumors (ROEC) in medically inoperable patients. Although these cases are rare, they could be the best indications for endobronchial BT.

Doing both for EBRT and BT with curative intent may bring advantage, because in these cases BT might be able to cover the whole ROEC target volume. The reported outcome in this selected group of patients is encouraging (Table 2).

#### **Combined radical treatment with external beam radiotherapy**

Fuwa *et al.* [21] treated 17 cases of ROEC with the combination of EBRT and intraluminal low-dose-rate brachytherapy (LDR-BT). Although doses of EBRT and LDR-BT varied considerably, no severe late toxicity was observed and 5-year cause specific survival was about 90%.

In a larger Japanese series reported by Saito *et al.* [22], 64 patients with ROEC (68 lesions) were treated with external beam RT to 40 Gy followed by 25 Gy LDR intraluminal brachytherapy. Five year survival was 72.3%, and disease free survival 87.3% with acceptable acute tox-

icity with 6% grade 2 pneumonitis and 29% grade 1 late stenosis, but without any grade 2 or greater deterioration of respiratory function due to radiotherapy. Nine (14%) local recurrences were seen, five of them rescued by surgery and EBRT.

In Europe, studies were performed on medically inoperable patients with HDR-BT alone [4,23-27]. Most patients received 3-6 fractions of 7-10 Gy at 10 mm from the source axis. Over 80% had a complete response and a good survival outcome. Local recurrences were noted in 5-40% of cases (Table 3). Acute toxicity was tolerable but fatal hemoptysis and bronchial necrosis were reported, especially in those patients who received more than 35 Gy HDR brachytherapy [24-27]. Groups of patients qualified for combined treatment (EBRT and BT) are heterogeneous (Table 3).

#### **Palliative endoluminal brachytherapy**

A lot of investigators have used a range of prescription points and fractional doses, which could not be directly compared.

As symptom relief is the main endpoint in palliative treatment, results should be described accordingly. There are subjective and objective methods for assessing

**Table 2.** Endobronchial high-dose-rate monotherapy for radiographically occult endobronchial carcinoma

Author	n	Clinical stage	Brachytherapy schedule (fr., dose)	Reference point	OFS (%)	CR (%)	LR (%)
Tredaniel <i>et al.</i> [27]	14	Limited to wall	3 × 7 Gy	10 mm	–	84	14
Ardiet <i>et al.</i> [23]	28	< 10 mm CT neg	3-5 × 7 Gy	10 mm	–	84	24
Perol <i>et al.</i> [26]	19	< 10 mm CT neg	3-5 × 7 Gy	10 mm	58 – 2y	83	5
Taulelle <i>et al.</i> [4]	22	Limited to wall	3-5 × 7-10 Gy	10 mm	46 – 3y	96	18
Hennequin <i>et al.</i> [24]	73	< 20 mm CT pos	5-6 × 7 Gy	5-15 mm	45 – 2y	NA	41
Marsiglia <i>et al.</i> [25]	34	2-40 mm	6 × 5 Gy	5-10 mm	78 – 2y	94	27

CT – computed tomography, OFS – overall free survival, CR – complete remission, LC – local control, HDR – high-dose-rate, y – years, Gy – Grey, fr. – fraction, neg – negative, pos – positive



**Table 3.** Curative high-dose-rate brachytherapy combined with external beam radiotherapy: in IIIA and IIIB lung cancers

Author	n	Clinical stage	EBRT (Gy)	Brachytherapy schemas (fr., dose)	LC (%)	OFS (%)
Mantz <i>et al.</i> [30]	39	T1-2 ≤ 5 cm	54-75.6	Trial: 1. 2-4 × 5-7 Gy 2. no BT	5 y: EBRT + BT – 58% EBRT – 32%	–
Huber <i>et al.</i> [51]	68	Advanced central lung tumors	60	Trial: 1. 2 × 4.8 Gy 2. no BT	5 vs. 3 mth ( <i>p</i> = 0.052)	10 vs. 8 mth ( <i>p</i> = 0.09)
Reddi <i>et al.</i> [52]	32	IIIA-IIIB	60	3 × 7.5 Gy	–	8 mth
Aygun <i>et al.</i> [53]	62	IIIA-IIIB	50-60	3-5 × 5 Gy	–	13 mth
Mehta <i>et al.</i> [54]	22	IIIA-IIIB	60	4 × 4 Gy	–	8.5 mth
Chang <i>et al.</i> [55]	54	IIIA-IIIB	20-70	3 × 7 Gy	–	–
Cotter <i>et al.</i> [56]	65	IIIA-IIIB	55-66	2-4 × 2.7-10 Gy	86%	8 mth
Speiser and Spratling [13]	50	IIIA-IIIB	60	3 × 7.5-10	80%	11 mth
Kohek <i>et al.</i> [57]	39	III	50-70	1-5 × 5.6	67%	13 mth
Zajac <i>et al.</i> [58]	24	III	50-61.2	3 × 5-10	82%	12 mth

LC – local control, OFS – overall free survival, BT – brachytherapy, LDR – low-dose-rate, MDR – medium-dose-rate, HDR – high-dose-rate, EBRT – external beam radiation therapy, y – years, Gy – Grey, mth – months, fr. – fraction

the efficacy of endobronchial brachytherapy. According to several large series published [13,50,55,57,59], overall symptom relief is achieved in more than two thirds of the patients. For example, in Kohek's series [57] relief from cough was obtained in 51/73, from dyspnea in 42/63, from hemoptysis in 6/8 patients. Improvement in general condition (Karnofsky scale) was noted in 69.5 to 76.5%.

Partial remission as assessed by objective measurements was achieved in 101/188, minor response in 25/188, no change in 29/188, progressive disease in 33/188 patients. Speiser and Spratling found a change in mean obstruction score (from bronchoscopy findings) before and after brachytherapy in 65 to 71% of the treated subgroups (curative, palliative, recurrent) [13].

Similarly, Gustafson *et al.* [31] noted significant clinical improvement in 74% of 38 symptomatic patients treated with 21 Gy at 1 cm, given in three HDR applications over 3 weeks. In patients without prior irradiation, there was a tendency for higher percentage of clinical and radiographic response. Authors concluded that a significant proportion of patients can be reduced asymptotically for the duration of their lives. In one of the largest published studies, there were 648 patients with endobronchial tumor treated with two different protocols of HDR brachytherapy [6].

Significant and durable clinical and radiographic responses could be obtained in patients with symptoms, despite prior radiation or metastatic and non-bronchogenic primary disease. There was no statistically important difference in the results between the two groups of patients treated with different doses. The complication rate compared favorably with those reported from other institutions. The median survival time of 5.9 months was consistent with the advanced stage of this population. Multivariate analysis

showed that the grade of remission after treatment, clinical stage, and performance status had maintained significance for survival time as well as for treatment response. Some published results are presented in Table 4.

#### *Endobronchial recurrence after external beam radiotherapy – endoluminal brachytherapy*

A special indication for endobronchial brachytherapy is recurrent endobronchial disease after EBRT in selected patients. Endobronchial radiation therapy, especially in previously irradiated area with dose limitations set by radiation tolerance of normal tissue, represents a therapeutic option with several advantages over conventional external beam radiotherapy and other therapeutic modalities. By placing a radioactive source near or in the tumor, a high dose of radiation is given to the tumor with the dose fall off in accordance with the inverse square law. The chance of damaging healthy tissues is reduced, since only a small amount of tissue receives therapeutic radiation dose [1]. Speiser and Spratling [13] reported the same palliative effect and survival outcome in these recurrences, as was seen in patients treated primarily with palliative intent. Gauwitz *et al.* [62] reported on 24 patients with recurrent disease after external beam RT of at least 55 Gy. All patients had an ECOG performance less than 2. Treatment consisted of 2 HDR fractions of 15 Gy at 6 mm (corresponding to 9 Gy at 10 mm). Symptomatic relief was obtained in 21/24 (88%), and relief from atelectasis in 15/18 (83%), lasting for 26 weeks on the average (7-40 weeks). Only 1 of 24 patients died of hemoptysis. Micke *et al.* [69] reported the results of HDR brachytherapy in 16 patients with recurrent lung cancer after EBRT (50-60 Gy). The recurrences were treated using 2 to 4 applications of 5 to 6 Gy each. The median period of remis-

**Table 4.** Palliative high-dose-rate brachytherapy of lung cancer – treatment results

Author	n	HDR doses (*)	Clinical improvement (%)	Chest X-ray improvement (%)	Bronchoscopy improvement (%)	Median OS
Bedwinek <i>et al.</i> [60]	38	3 × 6	76	64	82	10 mth
Jacobson <i>et al.</i> [61]		3 × 6	74	–	65	–
Gauwitz <i>et al.</i> [62]	24	–	88	–	88	8 mth
Sutedja <i>et al.</i> [19]	31	3 × 10	82	–	–	7 mth
Burt <i>et al.</i> [63]	50	1 × 15-20	50-86	46	88	–
Miller and Phillips [64]	88	3 × 10	–	–	80	–
Aygun <i>et al.</i> [53]	62	3-5 × 5	–	36	76	–
Mehta <i>et al.</i> [65]	31	4 × 4	88	71-100	85	–
Speiser and Spratling [66]	144 151	3 × 10 3 × 5-7	85-99	–	80	–
Zajac <i>et al.</i> [58]	82	1-5 × 10	82	–	74	–
Chang <i>et al.</i> [55]	76	3 × 7	79-95	–	87	–
Deldos <i>et al.</i> [67]	81	1-2 × 15	85	75	80	–
Gollins <i>et al.</i> [59]	406	1 × 10-20	–	–	65	–
Macha <i>et al.</i> [50]	365	3-4 × 5	66	–	–	–
Kelly <i>et al.</i> [68]	175	2 × 15	66	–	78	6 mth
Skowronek <i>et al.</i> [6]	303 345	3 × 7.5 1 × 10	88.4 (14.5% – 1 year)	–	No difference	3.7 mth

\*Number of fractions and fraction size in Gy, HDR – high-dose-rate brachytherapy, mth – months, OS – overall survival, fr. – fraction

sion was 4 months, whereas the median survival time was 9 months. Ornel *et al.* [70] have undertaken a prospective analysis of symptom response, duration response, and prognostic factors in 117 patients treated with brachytherapy. A single dose of 15 Gy was applied. Ninety-two patients had received previous EBRT. The median survival time was 12 months. There was no correlation between the total dose of the prior EBRT and the survival rate or rate of fatal hemoptysis. In the Bedwinek *et al.* [60] series, 38 patients were treated with high dose rate endobronchial brachytherapy to palliate symptoms caused by endobronchial recurrence of previously irradiated (> 50 Gy) lung cancer. Twenty-nine (76%) patients had symptomatic improvement in response to a dose of 18 Gy, given in 3 HDR sessions weekly. The median duration of symptoms relief was 7.5 months. Bronchoscopy carried out 3 months after brachytherapy revealed that 41% had complete regression and another 41% had partial regression.

In selected small tumors, palliation may be more successful and long term survivors have been described. At Manchester's Christie Hospital, 37 patients with small tumors less than 2 cm were treated with a single dose of 15-20 Gy delivered at 1 cm from the source [59]. Symptom relief lasting for up to 12 months after treatment was obtained for hemoptysis in 96%, relief of pulmonary collapse in 69%, relief of cough in 55%, and of dyspnea in 52%. The median survival was 709 days, 2-year survival (49.4%), and 5-year survival (14.1%).

### Interstitial brachytherapy

In early-stage of NSCLC, the addition of intraoperative brachytherapy to sublobar resection improved predicted rates of local control, and overall survival compared to sublobar resection alone. In more advanced disease with residual tumor or positive lymph nodes at surgery, the addition of thoracic brachytherapy resulted in favorable rates of local control and survival. When planar <sup>125</sup>I implants were placed, following resection of metastatic and locally invasive paraspinal tumors, excellent local control rates with minimal toxicity were seen, despite high localized doses to the spinal cord [1,37].

Interstitial brachytherapy as an independent radical brachytherapy was used so far in small groups of patients. Three presented in Table 5 reports come from studies of one group of researchers. They described in each of these papers different groups of patients in clinical stage I and II, III and a group of patients with Pancoast tumor [39,40,46]. In the last group, especially noteworthy are good clinical results: 70% local control in 5-years follow-up, 10 years survived (20% of patients) [39]. Published treatment results are presented in Table 5. In Figures 8-10, examples of treatment plan using <sup>125</sup>I are presented.

### Side effects

Acute side effects related to the treatment procedure itself are reported in 1-3% of applications consisting of

**Table 5.** Clinical results of interstitial brachytherapy

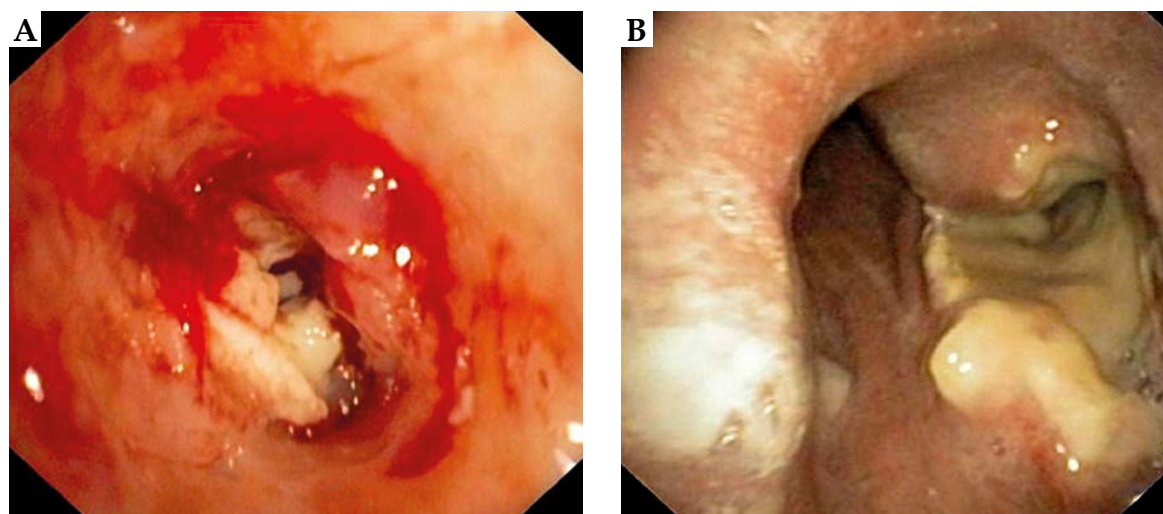
Author	Number of patients, clinical stage	Isotope, technique	LC	OS
Hilaris <i>et al.</i> [46]	322, stage III – N0	<sup>125</sup> I, residual tumor after surgery	71% – 2 y	20% – 2 y
Hilaris <i>et al.</i> [39]	55, stage I and II	<sup>125</sup> I, 24 patients – additional EBRT	T1N0 – 100% (5 y) T2N0 – 70% T1-2N1 – 71%	33% – 5 y
Hilaris <i>et al.</i> [40]	127, superior sulcus tumors – Pancoast tumors	Preoperative EBRT + partial resection + <sup>125</sup> I or <sup>192</sup> Ir	70% – 5 y	20% – 10 y
Fleishman <i>et al.</i> [38]	stage I	<sup>125</sup> I	71% – 1 y	median – 15 mth
Burt <i>et al.</i> [63]	stage III: 1. S only – 49 2. S incomplete + BT – 33 3. BT only – 101	<sup>125</sup> I	–	2 y; 3 y: 1 – 29%, 21% 2 – 30%, 22% 3 – 21%, 9%
Chen <i>et al.</i> [42]	23, I stage NSCLC, high risk group	Video-assisted thoracoscopic resection (VATR) + <sup>125</sup> I	Median follow-up – 11 mth	3 – metastases 3 – perioperative deaths 1 – recurrence
D'Amato <i>et al.</i> [43]	14, T1N0, NSCLC	Video-assisted thoracoscopic (VATS) wedge; resection + <sup>125</sup> I (Vicryl)	Median follow-up – 7 mth	No recurrences
Trombetta <i>et al.</i> [44]	278	Gross total resection of a non-small cell lung cancer using segmental resection, wedge resection, or sublobar resection + <sup>125</sup> I	Median follow-up – 45.3 mth	–

Y – years, EBRT – external beam radiation therapy, mth – months, S – surgery, BT – brachytherapy, NSCLC – non-small cellular lung cancer, LC – local control, OS – overall survival

pneumothorax, bronchospasm, hemoptysis, pneumonia, cardiac arrhythmia, cardiac arrest, or hypotension. Some problems arise in assessing the incidence of late complications occurring weeks to months after brachytherapy, as it is sometimes difficult to differentiate between complications due to tumor progression or from radiotherapy. Examples of late necrosis are presented in Figures 12.

Risk factors for severe hemoptysis include: received high dose of EBRT, several brachytherapy fractions, the

location of the tumor in the left upper lobe, long sections of irradiated bronchi (clinical stage). The rate of fatal hemoptysis reported in the literature varies from 0% to 18.9% (Table 6). However, it is recognized by most authors that most fatal hemorrhage is not due to brachytherapy but to tumor progression [24,60], and the rate is comparable to the incidence of hemoptysis after laser coagulation alone. Hennequin *et al.* [24] found no correlation with the site of the treatment, technical factors, fraction size, or associa-



**Fig. 12.** A, B) Irradiation effects after brachytherapy – partial remission, superficial necrosis with residual tumor issue [own material]

tion with EBRT as has been reported by others [59] but only with the length of endobronchial tumor spread. In the randomized trial conducted by the Munich group [51] however, fatal hemoptysis occurred more frequently after  $2 \times 4.8$  Gy HDR boost than in patients who did not receive a boost after 60 Gy EBRT (18.9% vs. 14.2% fatal hemoptysis) but results were not statistically significant ( $p = 0.53$ ).

The rate of tracheo-oesophageal fistula leading to death in the Macha [50] series is 5.3% (mean 3.5 months after start of radiotherapy). To prevent fistula, it seems to be important to examine the bronchial wall (e.g. flat ulceration) and the oesophageal wall (oesophagoscopy) carefully in central tumors growing in this area. Oesophageal

tumor infiltration carries a higher risk of developing fistula. Summarized observations are presented in Table 7.

Late effects such as chronic radiation bronchitis, bronchial stenosis, and tracheomalacia are of course only seen in long term survivors, most of them with lesions of the trachea or primary stem bronchus [24]. The incidence rates reported in the literature vary between 4 and 13%. Speisser and Spratling [13] related chronic bronchitis to dose and dose rate (9% in MDR and 13% in HDR). Hennequin *et al.* [24] found a relation between chronic bronchitis and trachea, and main stem sites ( $p = 0.002$ ), total dose ( $p = 0.04$ ), and irradiated volume ( $p = 0.02$ ), the latter being the only significant parameter in multivariate analysis.

**Table 6.** Incidence of massive hemoptysis after high-dose-rate endobronchial brachytherapy

Author	N	Dose HDR* (Gy)	EBRT** (n)	Reference point (mm)	Hemoptysis (%)
Nori <i>et al.</i> [71]	32	3-4 × 4-5	32	10	0
Speiser and Spratling [13]	295	3 × 10, 3 × 7.5	156	10	7
Chang <i>et al.</i> [55]	76	3 × 7	59	10	4
Gollins <i>et al.</i> [72]	406	1 × 15-20	82	10	7.9
Gustafson <i>et al.</i> [31]	46	3 × 7	12	10	7
Hennequin <i>et al.</i> [24]	149	4-6 × 7	112	5-15	7.4
Huber <i>et al.</i> [51]	56	2 × 4.8	56	10	18.9
Tredaniel <i>et al.</i> [27]	51	1-6 × 7	32	10	10
Ornadel <i>et al.</i> [70]	117	1 × 15	92	10	11
Tauelle <i>et al.</i> [4]	189	3-4 × 8-10	117	10	7
Kelly <i>et al.</i> [68]	175	1-4 × 15	160	6-7.5	5
Miller and Phillips [64]	88	3 × 10	-	10	0
Aygun <i>et al.</i> [53]	62	3-5 × 5	62	10	15

\*Number of fractions and fraction size in Gy, \*\*EBRT before BT or simultaneously  
EBRT – external beam radiation therapy, HDR-BT – high-dose-rate brachytherapy

**Table 7.** Incidence of fistulas after high-dose-rate and low-dose-rate brachytherapy

Author	n	Clinical stage	EBRT (Gy)	Brachytherapy schemas	Fistulas (n, %)
Macha <i>et al.</i> [73]	188	Recurrence after EBRT	–	3 × 7.5 Gy	15/188 (8.0%)
Harms <i>et al.</i> [10]	1. 21 2. 34	1. Recurrence after EBRT, metastases 2. Inoperable tumors	1. – 2. 30-60 Gy	1. 5-27 Gy 2. 10-20 Gy	1/55 (1.2%)
Deldos <i>et al.</i> [67]	81	Recurrence after EBRT	–	1-3 × 1.5 Gy (reference point at 6 mm)	1/81 (1.2%)
Cotter <i>et al.</i> [56]	65	Inoperable tumors	55-66 Gy	2-4 × 2.7-10 Gy	3/65 (4.6%)
Kohek <i>et al.</i> [74]	39	IIIA-IIIB	50-70 Gy	1-5 × 5.6 Gy	(2.5%)
Zajac <i>et al.</i> [58]	24	IIIA-IIIB	50-61.2 Gy	3 × 5-10 Gy	(8%)
Mehta <i>et al.</i> [65]	23	III	61 Gy	LDR – 48 Gy	(6%) – TV (3%) – TE
Sutedja <i>et al.</i> [75]	31	Inoperable tumors	–	3 × 10 Gy	3/31 (9.7%)
Schray <i>et al.</i> [76]	40	Inoperable tumors	–	LDR – 30 Gy	2/40 (5%)

TV – tracheovascular fistula, TE – tracheoesophageal fistula, EBRT – external beam radiation therapy, HDR – high-dose-rate, LDR – low-dose-rate

## Conclusions

Brachytherapy palliative treatment in advanced lung cancer is an efficient method that results in most of the patients in improvement of quality of their lives. Brachytherapy is relatively easy to perform on outpatients basis. Brachytherapy plays a limited but specific role in definitive treatment with curative intent in selected cases of early endobronchial disease as well as in the postoperative treatment of small residual peribronchial disease.

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## Disclosure

Author reports no conflict of interest.

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